Remarks

Reconsideration of this Application is respectfully requested.

Claims 30, 31, 36, 44-57, 61-63, 67, and 74-78 are pending in the application, with 30, 36, 67, 77 and 78 being the independent claims. Claims 46-54 and 61-63 stand withdrawn from consideration by the Examiner. Claims 77 and 78 are sought to be added. This amendment presents the claims in condition for allowance or in better form for consideration on appeal. These changes also are believed to introduce no new matter; and therefore, their entry is respectfully requested.

Consideration of the Declaration of Jorge F. Paniagua-Solis under 37 C.F.R. § 1.132 (attached hereto as EXHIBIT A) is respectfully requested under 37 C.F.R. § 1.116(e), as it contains evidence that is relevant to the presently outstanding rejections. Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. New Claims 77 and 78

The Examiner has indicated in the Office Action of December 15, 2006, that the specification as-filed is enabling for a composition comprising polyclonal $F(ab')_2$ antibody fragments capable of binding to a purified molecule or a mixture of antigenic molecules found in the venom of a scorpion. (Office Action of Dec. 16, 2006, p. 2 (hereinafter "OA")). Accordingly, Applicants have submitted new claims 77 and 78, which are directed to such compositions. Based in part on the Examiner's statement, Applicants respectfully assert that new claims 77 and 78 are in condition for immediate allowance.

II. Rejections under 35 U.S.C. § 112

The Examiner has rejected claims 30, 31, 36, 44, 45, 67 and 74-76 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not reasonably provide enablement for a *pharmaceutical* composition comprising polyclonal $F(ab')_2$ antibody fragments capable of binding to and neutralizing a purified molecule or mixture of antigenic molecules from the venom of a scorpion. (OA, p. 2 (emphasis in the Office Action)). More specifically, the Examiner asserts that there is an absence of specific and detailed information in the Applicants' specification of how to effectively use the *pharmaceutical* composition comprising the polyclonal $F(ab')_2$ antibody fragments as claimed. Further, the Examiner asserts that the "absence of working examples providing evidence which is reasonably predictive that the claimed *pharmaceutical* composition are effective for *in vivo* use, and the lack of predictability in the art at the time the inventions [*sic*] was made, an undue amount of experimentation would be required to practice the claimed *pharmaceutical* composition." (OA, p. 3). Applicants respectfully traverse this rejection and submit herewith for the Examiner's consideration, the Declaration of Jorge F. Paniagua-Solis under 37 C.F.R. § 1.132 (EXHIBIT A), which contains *in vivo* data demonstrating that the inventors have successfully generated $F(ab')_2$ antibody fragment *pharmaceutical* compositions according to the methods described in the specification, and that these compositions bind and neutralize scorpion venom in mice and humans, *i.e.*, they function in therapy. Below, the Applicants address each of

the factors set forth in *In re Wands*[1] (previously cited by the Examiner) in light of the data and remarks provided in EXHIBIT A. (*See* Office Action mailed March 21, 2006).

A. Breadth of the Claims

The Examiner asserts that based on the scope of the claim and "the number of possibilities associated with neutralizing an antigenic molecule," it would take undue experimentation to practice the claimed invention. (OA p. 3). Applicants respectfully traverse.

Contemplation of the entire specification demonstrates that the scope of the claimed subject matter is commensurate with the description of the presently-claimed invention, which is further validated by the *in vivo* data provided in the Declaration of Jorge Paniagua-Solis. (*See* EXHIBIT A). The objected to claims are directed to a *pharmaceutical* composition comprising $F(ab')_2$ antibody fragments that are capable of binding and neutralizing a purified antigenic molecule or mixture of antigenic molecules found in the venom of a scorpion. The data provided in EXHIBIT A demonstrates that $F(ab')_2$ antibody fragment *pharmaceutical* compositions prepared and administered *in vivo* intravenously or intraperitoneally according to the methods described in the specification of the present application to mice and humans successfully neutralized the venom of multiple scorpions within the family *Buthidae*, including those in the *Centruroides* and *Tityus* genera, as contemplated by the specification of the present application. (*See* EXHIBIT A, ¶¶6-24; *see also* specification, ¶¶ [0006], [0024-0026], [0040-0042], [0097 - 0101]). Accordingly, Applicants assert that the specification as-

[1] (1) the quantity of experimentation necessary, (2) the limited working examples, (3) the unpredictability of the art, (4) the lack of sufficient guidance in the specification and (5) the breadth of the claims. 585 F.2d 731, 737 (Fed. Cir. 1988).

filed provides an enabling disclosure consistent with the full scope of the presently-pending claims.

B. Guidance in the Specification

In the Office Action dated March 21, 2006, the Examiner asserted that "[t]he specification as filed does not provide a definition of 'neutralizing a purified antigenic molecule' in addition to [*sic*] insufficient guidance and direction to the nature, parameter and endpoints of 'neutralizing' the antigenic molecule." (OA, p. 4). In the Office Action of December 15, 2006, the Examiner appears to partially withdraw this rejection with regard to the definition of "neutralizing," but further asserts that there are no working examples showing that the claimed $F(ab')_2$ antibody fragment *pharmaceutical* compositions actually bind and neutralize scorpion venoms to achieve the therapeutic effect described on page 2 of the specification. (OA p.3). Applicants respectfully assert that the Examiner has conceded that the specification as-filed provides guidance with regard to "neutralizing a purified antigenic molecule," and that the specification is enabling for a composition comprising polyclonal $F(ab')_2$ antibody fragments capable of binding to the antigenic molecules found in the venom of a scorpion. (OA, p. 2).

Applicants address the existence of working examples below, but also point to the data provided in EXHIBIT A showing *in vivo* neutralization of the toxins found in scorpion venoms by the claimed pharmaceutical compositions when administered intravenously and intraperitoneally to mice and humans, as described in the specification. (*See* EXHIBIT A, ¶¶6-24; *see also* specification, ¶¶ [0038-0042], [0096], [0106-0108]). The specification describes that for pharmaceutical compositions against scorpions, "the $F(ab')_2$ preparation to be filled in each flask is the amount necessary to neutralize from

about 135 to about 220 lethal doses 50% of the venom," and goes on to describe pharmaceutically acceptable carriers for systemic or topical administration. (*See* specification, ¶¶ [0038-0041]). Further, the specification states that administration of the claimed pharmaceutical composition is normally systemic, whether intramuscular or intravenous, and that scorpion envenomation typically requires about 1 to 3 flasks of $F(ab')_2$ antibody fragment pharmaceutical composition. (¶[0042]). Finally, the specification describes *in vitro* and *in vivo* tests of the neutralizing capability of $F(ab')_2$ antibody fragment pharmaceutical compositions. (*See* specification, ¶¶ [0096], [0106-0108]). Thus, the specification describes methods for preparing, formulating, testing and administering the claimed polyclonal $F(ab')_2$ antibody fragment pharmaceutical compositions, and the data provided in EXHIBIT A confirms that the pharmaceutical compositions are effective for their claimed utility.

Accordingly, the Applicants assert that the specification provides sufficient guidance to enable the practice of the claimed invention by a person of ordinary skill in the art at the time of filing.

C. Existence of Working Examples

The Examiner has asserted that the specification as-filed does not contain working examples providing evidence that is reasonably predictive that the claimed *pharmaceutical* composition is effective for *in vivo* use, and that the *in vivo* experiment described in Example 7 of the instant application is insufficient because it discloses an *in vivo* experiment involving neutralization of a non-scorpion species. (OA, p. 3). Applicants respectfully traverse.

As discussed on page 14 of Applicants' Reply dated September 21, 2006, the specification as-filed provides working examples that correlate with the presently-pending claims, and therefore a person of ordinary skill in the art would have been able to carry out the present invention without undue experimentation. In addition to the *in vitro* and *in vivo* testing methods described in Examples 7 and 8 of the specification, EXHIBIT A, submitted herewith, provides *in vivo* data from tests conducted in mice and humans demonstrating the neutralization capabilities of $F(ab')_2$ antibody fragment pharmaceutical compositions against scorpion venoms, as recited in the presently pending claims. (EXHIBIT A, ¶¶6-24).

In one *in vivo* experiment, $F(ab')_2$ antibody fragments in a pharmaceutical composition made by the method described in the specification were shown to be effective in neutralizing the venom of the *C. sculpturatus* scorpion in mice. (EXHIBIT A, ¶9). Additionally, this experiment showed that the neutralizing ability of the claimed $F(ab')_2$ antibody fragment pharmaceutical composition exceeded the neutralizing ability required by the Mexican Pharmacopeia. (EXHIBIT A, ¶9).

The second set of *in vivo* experiments described in EXHIBIT A, characterized the neutralization capacity of the claimed $F(ab')_2$ antibody fragment pharmaceutical composition against *T. pachyurus pocock* scorpion venom, and demonstrated that the composition was effective for neutralizing scorpion venom in mice. (EXHIBIT A, ¶¶10-16).

The third set of *in vivo* experiments described in EXHIBIT A demonstrated the efficacy of the claimed $F(ab')_2$ antibody fragment pharmaceutical composition in humans. (EXHIBIT A, ¶¶ 17-24). The experiment involved the participation of 15

children who presented to hospitals in Arizona with systemic signs of scorpion envenomation. (*Id.*) All the patients received intravenous midazolam sedation (standard of care) prior to enrollment in the study, followed by intravenous administration of either placebo or the claimed $F(ab')_2$ antibody fragment scorpion pharmaceutical antivenom composition. (*Id.*) A combination of physical assessments and measurements of blood venom and antivenom levels demonstrated that $F(ab')_2$ antibody fragment antivenom pharmaceutical composition prepared according to the method described in the present application is effective for *in vivo* use, with an extremely high rate of successful resolution of symptoms associated with envenomation in both species. (*Id.*)

It is important to note that each of the experiments described above and in EXHIBIT A were conducted over time periods that did not exceed those which would typically be expected when measuring efficacy of an pharmaceutical antivenom composition *in vivo*. (EXHIBIT A, ¶¶ 9, 15 and 18). Thus, the time periods required to practice the claimed invention also weigh against the Examiner's assertion of undue experimentation.

The *in vivo* experiments and data produced by the administration of the claimed $F(ab')_2$ antibody fragment pharmaceutical composition, as described in EXHIBIT A, provide evidence that the examples and descriptions in the specification as-filed demonstrate to one of ordinary skill in the art that $F(ab')_2$ antibody fragments can be used to neutralize, *in vivo*, antigenic molecules found in the venom of a scorpion in mice and humans. Therefore, Applicants assert that a person of ordinary skill in the art at the time of filing could have practiced the present invention without undue experimentation, in light of the working examples and description provided in the specification.

D. Predictability in the Art

The Examiner has reiterated the assertion from the previous Office Action that, "[i]t is at issue whether or not the claimed invention would function as a pharmaceutical composition." (OA, p. 3). Further, the Examiner argues that "not all antibodies are neutralizing," and that "not all animal venoms are equally feasible in prophylactic measures." (OA, p. 3). Additionally,

> [g]iven the number of possibilities associated with neutralizing an antigenic molecule, including via direct or indirect effects associated with antigenic structure or function, as to whether such a desired effect can be achieved or predicted, as encompassed by the claim, it would take undue experimentation to practice the claimed invention.

(OA, p. 3). Applicants respectfully traverse.

Regardless of the level of predictability in the relevant field prior to the filing date of the present application, Applicants provided in the specification the methodolgy to reproducibly produce pharmaceutical compositions of $F(ab')_2$ antibody fragments capable of neutralizing antigens found in scorpion venom, and confirmed that they worked. (*See* specification, ¶¶ [0097-0102], *see also* Exhibit A, ¶¶6-24). Thus, a person of ordinary skill in the art could have readily practiced the claimed invention without undue experimentation at the time of filing.

E. Quantity of Experimentation Needed to Practice the Present Invention

The Examiner has asserted that based on the "undue amount of experimentation [that] would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success," the specification does not enable any person skilled in the art to which it pertains to make and/or use the invention commensurate in scope with the pending claims. (OA, p. 2-3). Applicants respectfully traverse.

A person of ordinary skill in the art could have practiced the present invention without undue experimentation at the time of filing, based on the guidance in the specification and the level of skill in the art, as is shown by the experiments described in EXHIBIT A, submitted herewith. The standard for enablement is defined as a "lack of undue experimentation." *See*, e.g., *In re Wands*, 858 F.2d at 737. A "reasonable expectation of success" is *not* the standard for enablement, but rather is a component of the analysis of obviousness under 35 U.S.C. § 103. *See*, e.g., *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988). Thus, the Examiner has applied the incorrect standard. When the appropriate standard is applied, it is clear that no undue experimentation was required for a person of ordinary skill in the art to practice the claimed invention at the time of filing.

In this case, while the claimed $F(ab')_2$ antibody fragment pharmaceutical composition would not have been obvious to a person of ordinary skill in the art at the time of filing, the description of the invention provided by the specification as-filed would have enabled such a person to practice the claimed invention without undue experimentation, which is demonstrated by the experiments described in EXHIBIT A. More specifically, the Applicants applied the methods described and exemplified in the specification to make the polyclonal $F(ab')_2$ antibody fragment pharmaceutical composition recited in the presently-pending claims, and successfully used the pharmaceutical composition *in vivo* in mice and humans. (*See* Specification, Examples 1-2, 7, 8; *see also* EXHIBIT A, ¶¶ 6-24). There is nothing to suggest that an undue amount of experimentation was necessary to make and/or use the presently-claimed invention, and produce the data disclosed in EXHIBIT A. (*Id.*) Thus, any experimentation required to

practice the present invention would have been reasonable, not undue. Applicants respectfully request that this rejection be reconsidered and withdrawn.

In summary, claims 30, 31, 36, 44, 45, 67 and 74-78 are fully enabled by the specification as-filed, as is evidenced by the experimental data provided in EXHIBIT A. The Examiner has not provided any specific evidence to the contrary, therefore there is no reason to doubt Applicants' assertion that the claimed $F(ab')_2$ antibody fragments are fully enabled as a pharmaceutical composition that is able to bind to a scorpion venom. *See In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971)("[I]t is incumbent upon the Patent Office . . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.")(emphasis in original); *see also In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). Therefore, Applicants respectfully request reconsideration and withdrawal of the present invention.

III. Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 30, 31, 36, 44, 45, 67 and 74-76 under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 5,443,976 (hereinafter "the '976 patent"), in view of U.S. Patent No. 4,849,352 (hereinafter "the '352 patent"), as evidenced by Harlow and Lane (*Antibodies*, Harlow, E. and Lane, D., eds., Cold Spring Harbor Laboratory Pres, pp. 298-99)(1988)(hereinafter "Harlow"), and Campell (*Monoclonal and Immunosensor Technology*, Campbell, A., ed., Elsevier Science, pp. 288-91)(1991)(hereinafter "Campbell"). (OA, p. 4). More specifically, the Examiner alleges that one of ordinary skill in the art would have been motivated to combine the pepsin digestion and ammonium sulfate purification taught by the '352 patent, with the

polyclonal and polyvalent antibody to scorpion venom taught by the '976 patent, to produce more readily utilizable antibody to scorpion venom. (OA, pp. 5-6). Applicants respectfully traverse this rejection.

The Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the cited art. *See In re Piasecki*, 745 F.2d 1468, 1471-72 (Fed. Cir. 1984). A *prima facie* case of obviousness cannot be established unless all of the claim elements are taught or suggested by the cited references. *See In re Royka*, 490 F.2d 981, 984-85 (CCPA 1974); *see also In re Glaug*, 283 F.3d 1335, 1341-42 (Fed. Cir. 2002); *In re Rijckaert*, 9 F.3d 1531, 1533 (Fed. Cir. 1993). The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986). In this case, the Examiner's burden has not been satisfied because there was no reasonable expectation that a person of ordinary skill in the art could have combined the teachings of the '976 patent with the '352 patent to successfully arrive at a pharmaceutical composition comprising polyclonal $F(ab')_2$ antibody fragments capable of binding to a purified molecule or mixture of antigenic molecules found in the venom of a scorpion, as recited in the presently-pending claims.

The Examiner admits that the '976 patent does not teach $F(ab')_2$ antibody fragments, but instead discloses IgY polyclonal antibody to a scorpion venom. (OA, p. 5). Also, according to the Examiner, "the '352 patent teaches a pharmaceutical composition comprising a polyclonal $F(ab')_2$ [that] binds to any antigen." (OA, p. 5). However, the '352 patent does not disclose a pharmaceutical composition comprising polyclonal $F(ab')_2$ antibody fragments capable of binding to a purified molecule or

mixture of antigenic molecules found in the venom of a scorpion, as recited in the presently-pending claims.

In the outstanding Office Action, the Examiner states that "not all animal venoms are equally feasible in prophylactic measure," and that "not all antibodies are neutralizing," citing Burton *et al.* (of record) and Vanlandschoot *et al.* (of record). (OA, p.3). In a rejection of the presently-pending claims under 35 U.S.C. §112, first paragraph, the Examiner also stated that, "[i]n view of . . . the lack of predictability in the art at the time the inventions [*sic*] was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a *reasonable expectation of success*." (OA, p.3). In other words, the Examiner has conceded that person of ordinary skill in the art at the time of filing could not have made and/or used a pharmaceutical composition of $F(ab')_2$ antibody fragments capable of neutralizing the antigens found in scorpion venom, based on what was known in the art at that time, with a reasonable expectation of success.

However, as discussed above, once *the description provided in the present specification became available*, a person of ordinary skill in the art could have then readily practiced the claimed invention without undue experimentation at and after the time of filing. This was further demonstrated by the experiments and data provided in EXHIBIT A. Until Applicants provided the methodology to reproducibly produce pharmaceutical compositions of $F(ab')_2$ fragments capable of neutralizing antigens found in scorpion venom, and demonstrated that they worked, the field (as admitted by the Examiner) lacked the necessary expectation of success. Once Applicants showed success, however, the field has now become more reasonably predictable, due to

Applicants' own specification and data. At the filing date, however, the claimed $F(ab')_2$ compositions were non-obvious. Thus, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a)(or lack of enablement under 35 U.S.C. § 112, ¶1). Reconsideration and withdrawal of this rejection respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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